Updates of Lupus Nphritis

DR EHAB ELTORABY

Prof. Of Internal Medicine

Rheumatology & Immunology Unit

Mansoura Faculty Of Medicine

Lupus nephritis, one of the most serious manifestations of SLE, usually arises within 5 years of diagnosis; however, renal failure rarely occurs before American College of Rheumatology criteria for classification are met.

TABLE 1. 1997 Updated American College of Rheumatology criteria for classification of systemic lupus erythematosus. (Adapted with permission of John Wiley & Sons, Inc from: Tan EM et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982 Nov;25(11):1271-7 and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997 Sep;40(9):1725.)

Criteria		Brief definition notes
1	Malar rash	
2	Discoid rash	
3	Photosensitivity	Patient history or physician observation
4	Oral ulcers	Oral **or** nasopharyngeal
5	Non-erosive arthritis	Tenderness, swelling or effusion in ≥2 peripheral joints
6	Pleurisy or pericarditis	Pleurisy: convincing history of pleuritic pain, pleural rub, or effusion **or** pericarditis: ECG evidence, rub, or effusion
7	Renal	Persistent proteinuria (>0.5 g/day or >3+ by dipstick) **or** cellular casts on microscopy (red, granular, tubular or mixed)
8	Neurological	Seizures or psychosis in the absence of drugs or metabolic derangements
9	Haematological	At least 1 of: • Haemolytic anaemia with reticulocytosis • Leucopenia (<4000/mm³) on ≥2 occasions • Lymphopenia (<1500/mm³) on ≥2 occasions • Thrombocytopenia (<100,000/mm³) without drug cause
10	Immunological	At least 1 of: • Anti-DNA antibody • Anti-Smith antibody • Positive antiphospholipid antibodies identified by: – abnormal serum level of IgM or IgG anticardiolipin antibodies – positive lupus anticoagulant
11	Positive ANA	

At least 4 criteria are needed for the classification of SLE.

ANA antinuclear antibodies; DNA deoxyribonucleic acid; ECG electrocardiogram; Ig immunoglobulin

SLICC† Classification Criteria for Systemic Lupus Erythematosus

RheumTutor.com

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

- the GFR may be still preserved while there is severe inflammation thus making it difficult to assess its true changes

- For example, in a 25-year-old, 50-kg woman with lupus nephritis, an increase in the serum creatinine from 0.6 mg/dL to 0.9 mg/dL (estimated GFR change from 114 to 75 mL/min), with both levels in the normal laboratory range, represents a 35% reduction in function

- Proteinuria may take weeks to months to normalize, or not normalize at all, irrespective of immunologic or inflammatory activity

- Distinguishing the relative extent of ongoing inflammation from chronic fibrotic disease may be especially difficult

DNA → RNA → Proteins

Genome → Transcriptome → Proteome

CGTCCAACTGACG
TCTACAGGCTTAT
TTAGCGCTATAAG
TATATATAGGCGA
AGTCATACCTGTA
ATTCGCCAGTAGT
TACGTGACAGTCC
GGCTATCCACCAT
TACCCGGGTAT.....

DNA sequencing

cDNA arrays

2D-PAGE ?

BIOMARKERS FOR RENAL INVOLVEMENT

- Most lupus nephritis patients have antichromatin / nucleosome antibodies and they may be **positive** when the anti-dsDNA antibodies are negative.

- Similar findings were observed with anti-C1q antibodies especially with **nephritic** flares.

- Anti-α actinin antibodies are prevalent in patients with active **lupus nephritis**, and they may be more predictive of nephritis than anti-dsDNA antibodies.

- Adrenomedullin released from macrophages and smooth muscle cells is elevated in SLE, pregnancy, hypertension with left ventricular hypertrophy, diabetes, and other chronic diseases, and it appears to be elevated in ***active lupus nephritis***

URINE BIOMARKERS

- Endothelial-1
- Lipocalin-2 (neutrophil gelatinase-associated lipocalin)
- U-MCP-1 (urinary monocyte chemoattractant protein–1)
- Migration inhibition factor
- Adiponectin
- VCAM-1 (vascular cell adhesion molecule-1)
- P-selectin
- CXCL-16 (C-X-C chemokine ligand 16)
- FOXP3 (forkhead family transcription factor 3)
- TWEAK (tumor necrosis factor–like weak inducer of apoptosis)
- Osteoprotegerin

Endothelial-1

- It is a 21–amino acid peptide produced in the vasculature, and it participates in cell proliferation, inflammation, vasoconstriction, and fibrosis.
- Urinary ET-1 reflects both renal and extrarenal production.
- UrinaryET-1 increased in CKD, RA, and SLE.
- Decreased after therapy in lupus nephritis

Lipocalin-2 (NGAL)

- Neutrophil Gelatinase-Associated Lipocalin secreted by leukocytes and epithelial cells & is important for iron transport.

- Urinary levels were found to be predictive of active nephritis

Urinary MCP-1

monocyte chemoattractant protein–1

- Has also been demonstrated to be predictive of disease activity.
- Increased levels were found to precede lupus flare by as much as 4 months, and urinary MCP-1 fell with successful treatment.

VCAM-1

- Found mostly in the kidney, recruits monocytes, dendritic cells, and endothelial cells to inflamed areas.

- Urinary excretion of VCAM-1 increased in lupus patients compared with the other groups.

Osteoprotegerin

- Tumor necrosis factor family causes bone resorption and is found in many other organs.
- Urinary levels of osteoprotegerin correlate well with the presence of renal lupus but not with the severity of disease

NON-INVASIVE RENAL PROTEIN BIOMARKERS ARE ASSOCIATED WITH HISTOLOGICAL FEATURES OF LUPUS NEPHRITIS *Hermine et al 2013 Arth Rheum*

Biomarkers‡ / Histological features	NGAL	MCP1	CP	AAG	TF	L-PGDS	C3	C4	P/C-ratio	GFR	Serum creatinine
Mesangial proliferation		●	●	●	●						
Capillary proliferation		●	●		●						
Cellular crescents	●			●	●						
Fibrinoid necrosis			●								
Wire-loops										●	
BAI Score		●	●	●	●				●		
Fibrosis											●
Tubular atrophy						●					
BCI Score										●	●
Epimembranous deposits											
Class 5 lupus nephritis										●	

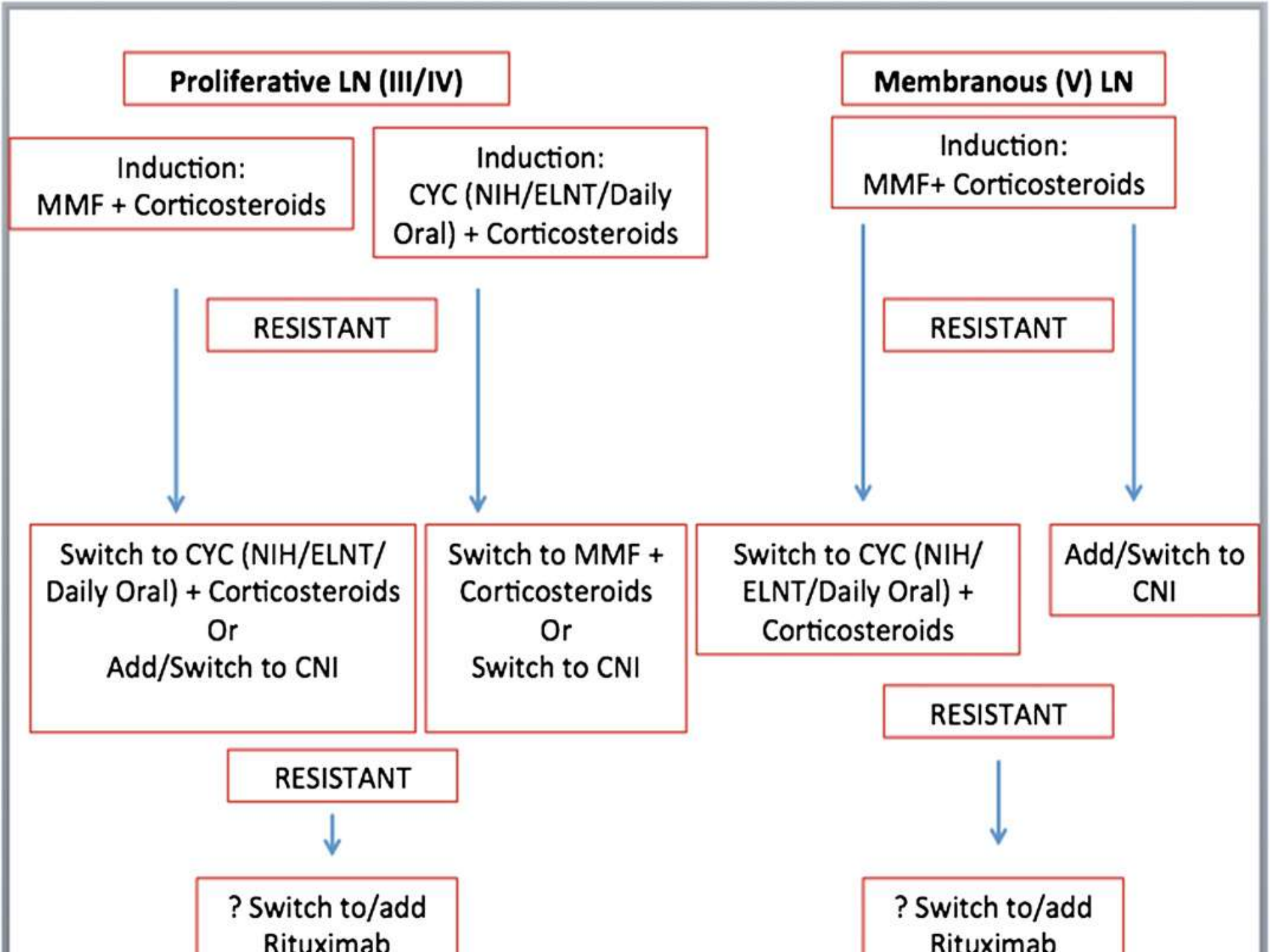
Lupus nephritis urinary proteome

- α-1 Acid glycoprotein
- α1 Microglobulin
- Zinc α-2 glycoprotein
- IgG κ light chain
- α-1 Antitrypsin
- Albumin
- Hepcidin-20
- Aldolase A

Updates In Treatment

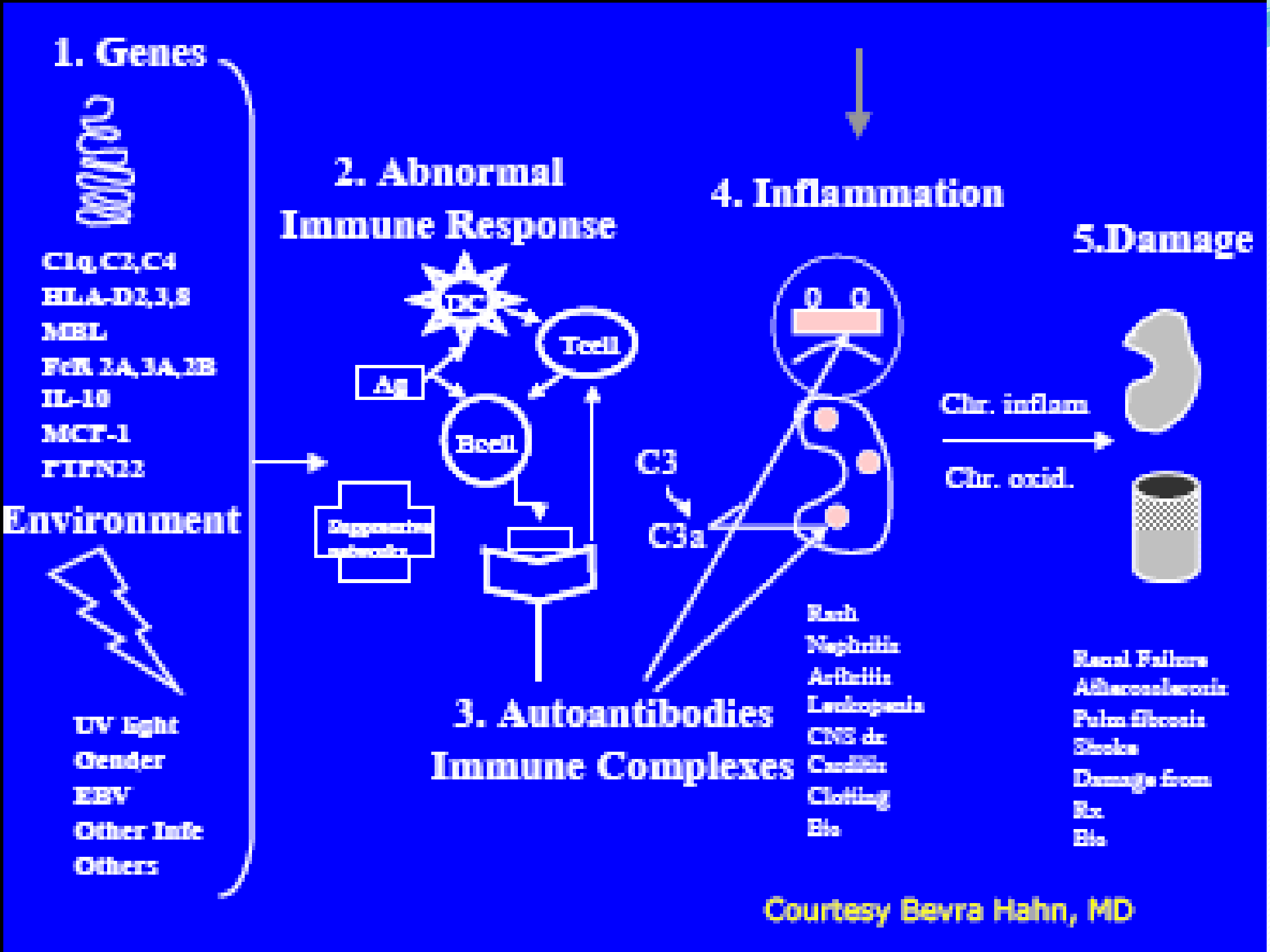
Aims of care in lupus nephritis

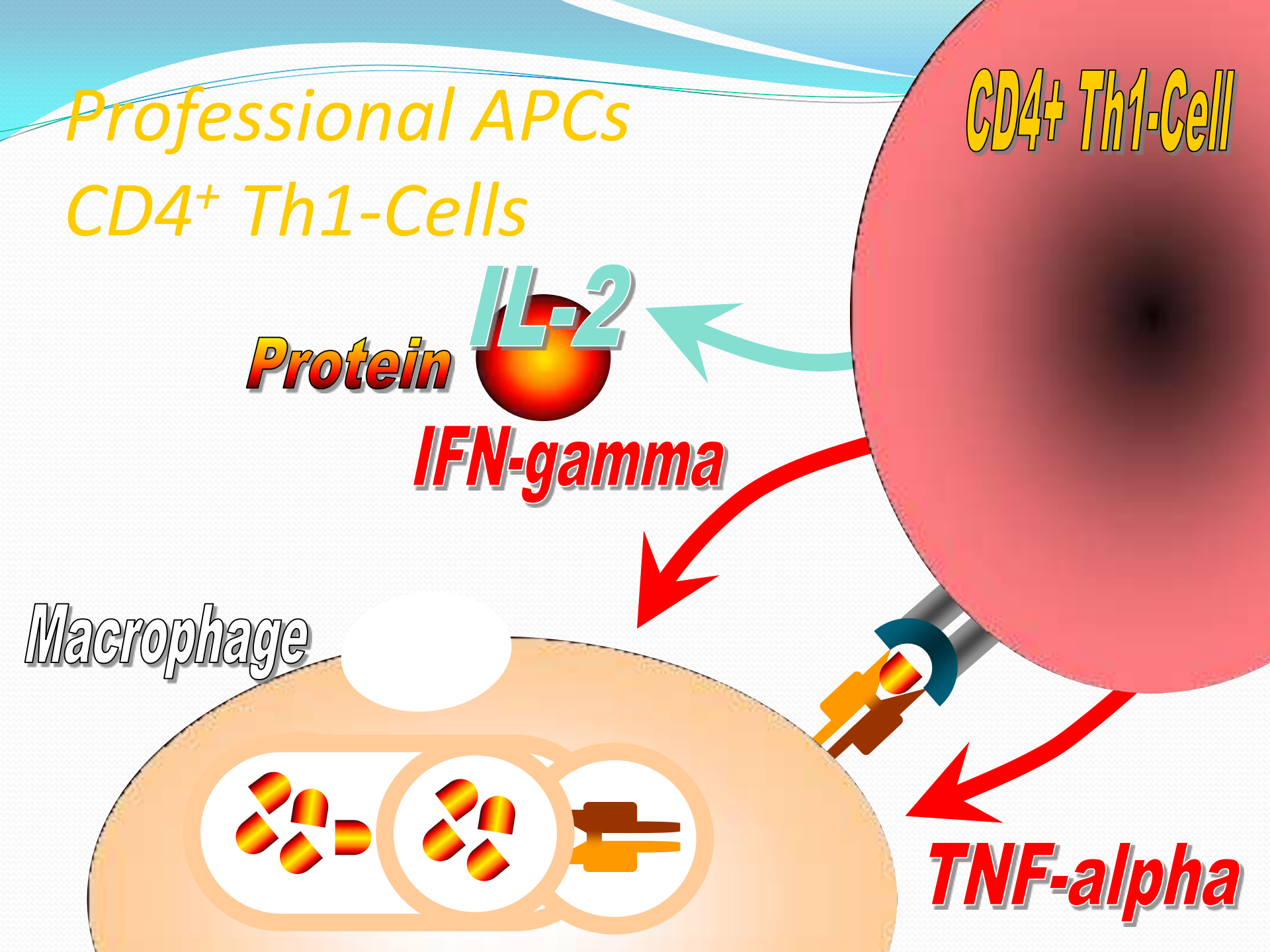
- Obtain a complete remission
- Maintenance of renal function
- Reduction of renal (especially nephritic) flares
- Control of proteinuria
- Control of blood pressure
- Control of vascular risk factors
- Identification and treatment of APL S
- Minimization of treatment-related toxicity
- Assessment of infection risk
- Bone protection
- Role of adjunctive therapies
- Assessment and maximization of compliance
- Overall reduction of mortality


Proliferative LN (III/IV)
Induction:
MMF + Corticosteroids
Induction:
CYC (NIH/ELNT/Daily Oral) + Corticosteroids
RESISTANT
Switch to CYC (NIH/ELNT/ Daily Oral) + Corticosteroids
Or
Add/Switch to CNI
Switch to MMF + Corticosteroids
Or
Switch to CNI
RESISTANT
? Switch to/add Rituximab
Membranous (V) LN
Induction:
MMF+ Corticosteroids
RESISTANT
Switch to CYC (NIH/ ELNT/Daily Oral) + Corticosteroids
Add/Switch to CNI
RESISTANT
? Switch to/add Rituximab

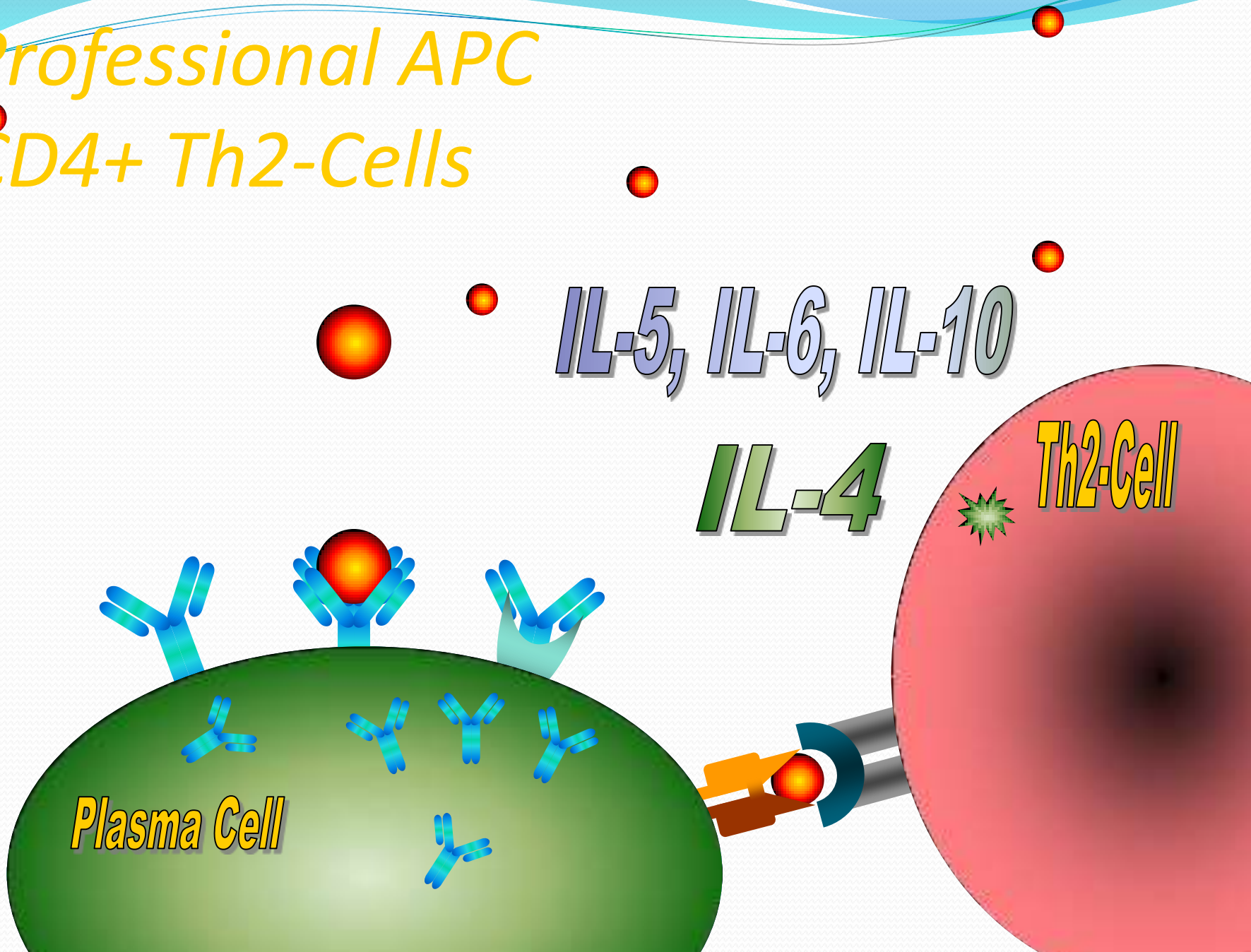
Steps for drug approval

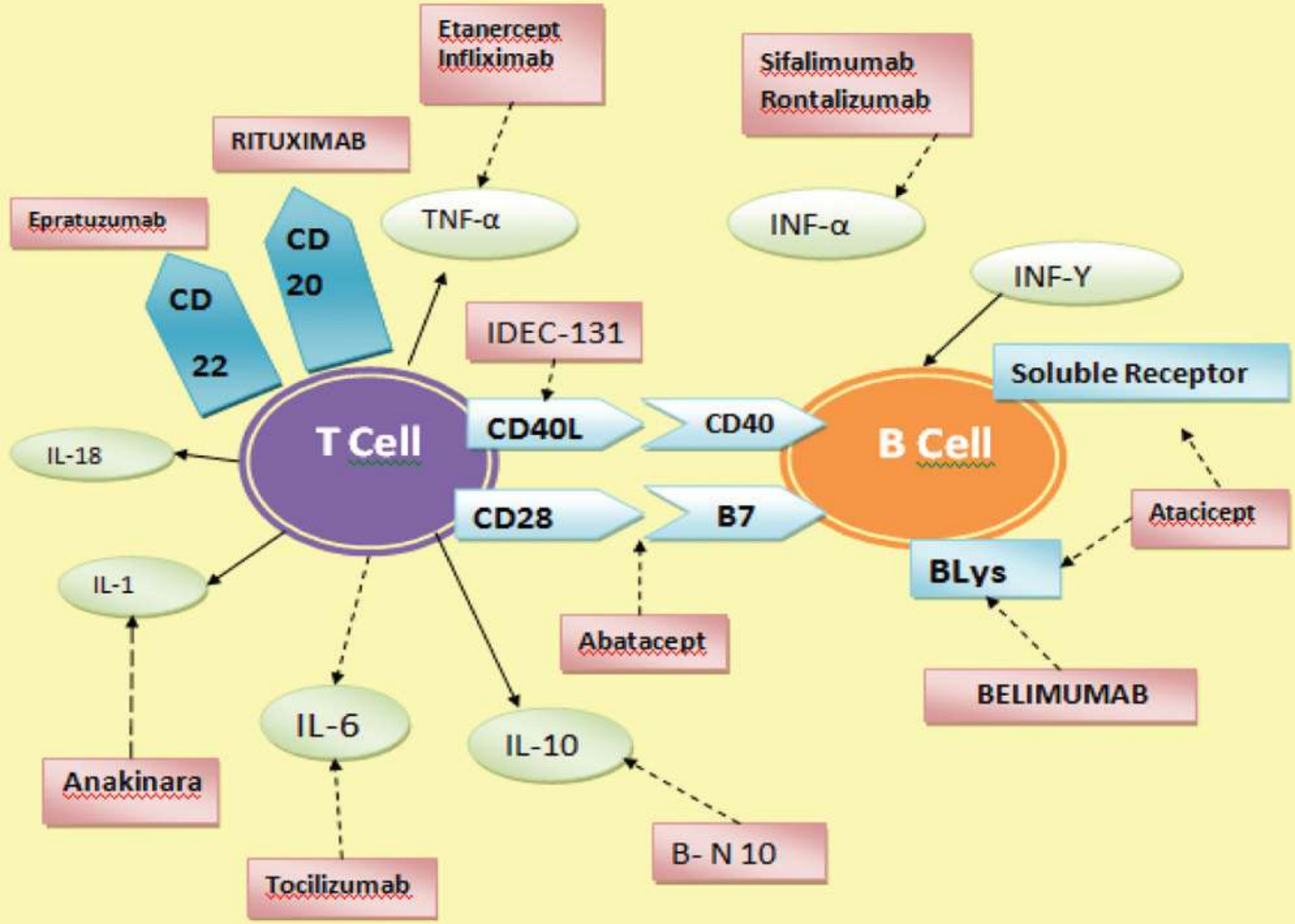
- Pre-clinical studies – Non-Human
- Phase I studies – 1st time in humans <100 people
  - What are the side effects and what dose should be given?
- Phase II studies – 100+ people
  - Does the drug work and are there other side effects?
- Phase III studies – 1000+ people
  - Does the drug work and is it safe long term?


1. Genes
C1q,C2,C4
HLA-D2,3,8
MBL
FcR 2A,3A,2B
IL-10
MCP-1
PTPN22
Environment
UV Light
Gender
EBV
Other Infe
Others
2. Abnormal
Immune Response
DC
Tcell
Ag
Bcell
Suppressor
4. Inflammation
C3
C3a
3. Autoantibodies
Immune Complexes
Rash
Nephritis
Arthritis
Leukopenia
CNS dz
Carditis
Clotting
Dia
5.Damage
Chr. inflam
Chr. oxid.
Renal Failure
Atherosclerosis
Pulm fibrosis
Stroke
Damage from
Rx
Dia
Courtesy Bevra Hahn, MD

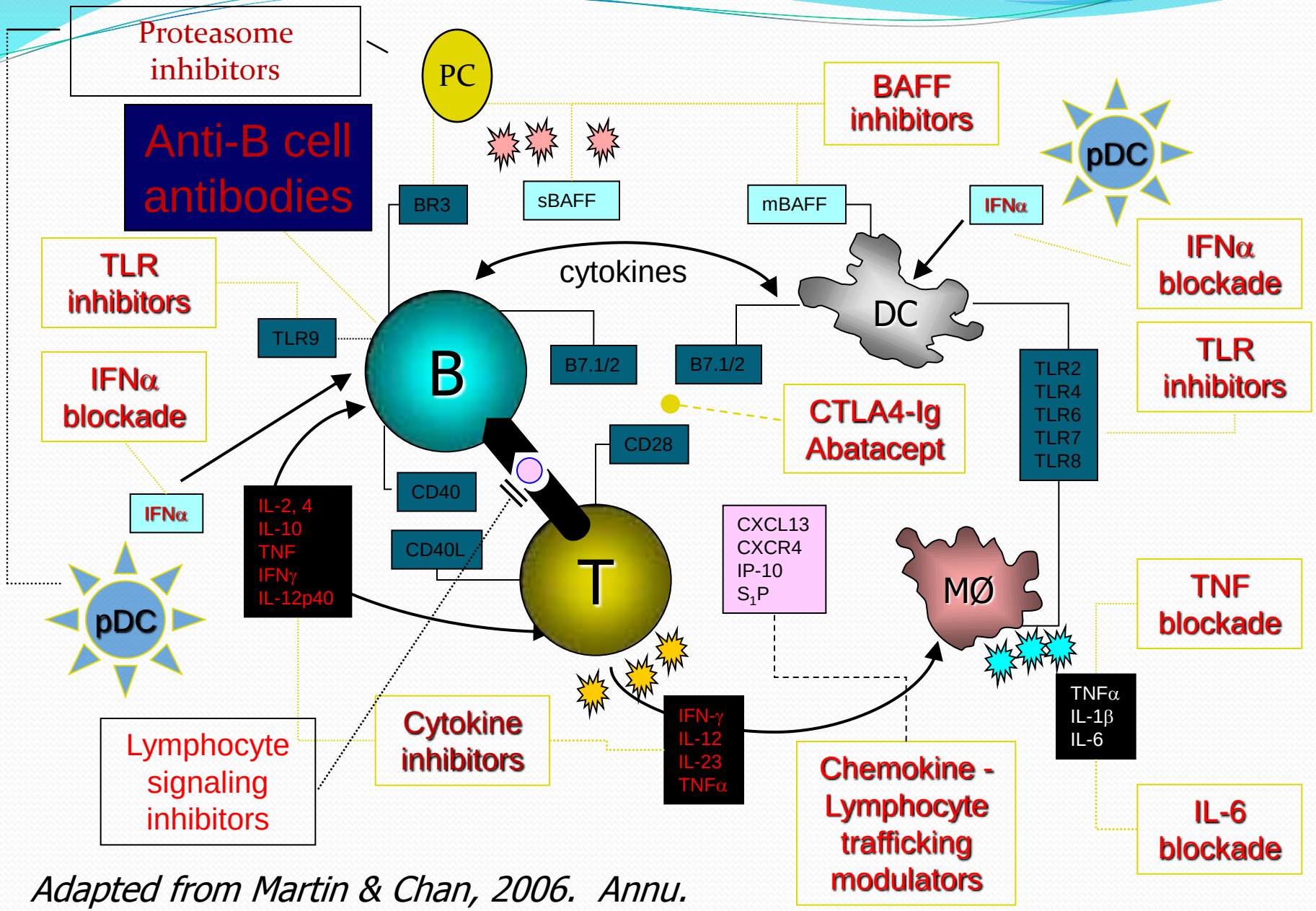

Professional APCs
CD4+ Th1-Cells
CD4+ Th1-Cell
IL-2
Protein
IFN-gamma
Macrophage
TNF-alpha

Professional APC
CD4+ Th2-Cells




Etanercept
Infliximab
Sifalimumab
Rontalizumab
RITUXIMAB
Epratuzumab
TNF-α
INF-α
CD 20
CD 22
INF-Y
IDEC-131
Soluble Receptor
T Cell
CD40L
CD40
B Cell
IL-18
CD28
B7
Atacicept
IL-1
BLys
Abatacept
BELIMUMAB
IL-6
IL-10
Anakinara
B- N 10
Tocilizumab

Treatment of SLE: Into the 21st Century

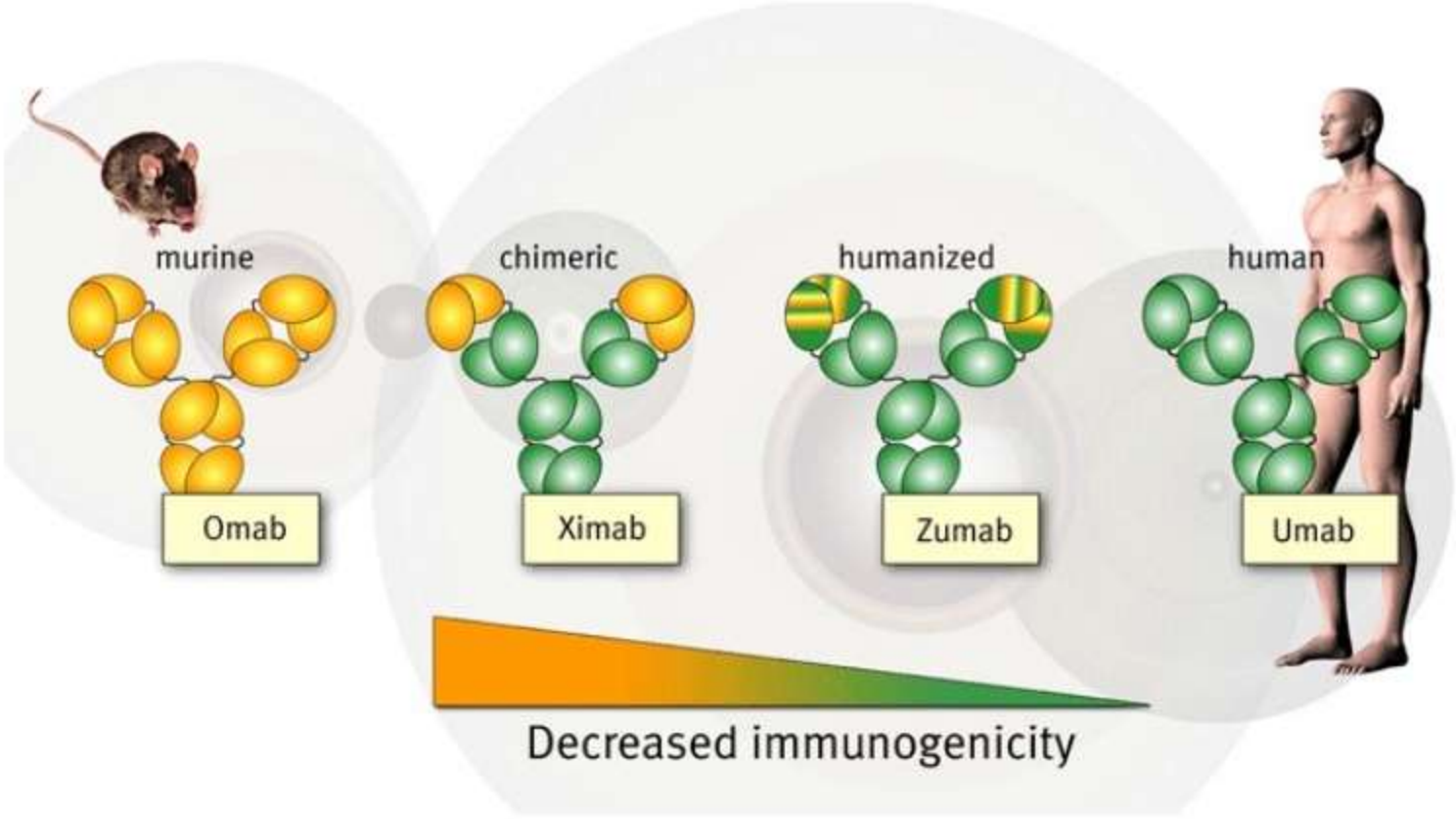


Adapted from Martin & Chan, 2006. Annu. Rev. Immunol. 24:467-96

NHS Education for Scotland

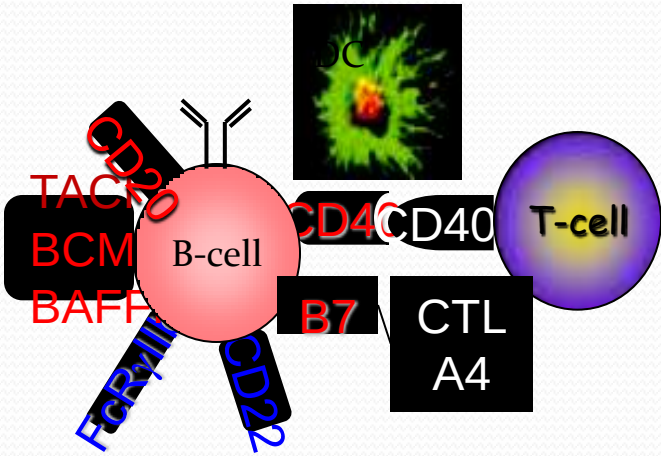
Pharmacy

Immunogenecity



New biologic therapies under study in SLE

- B cell elimination:
  - B cell depleting: anti-CD20
  - B cell depleting/modulating: anti-CD22
  - Specific autoreactive B cell depletion: LJP394
- Co-stimulatory blockade:
  - anti-CD40L, CTLA4-Ig, anti-ICOSL
- Other: anti-cytokine, anti-survival factors, factors up-stream and down-stream of B cells
  - anti-BAFF, TACI-Ig
  - anti-IL-10, anti-IL-6
  - anti-IFN
  - anti-TNF
  - anti-CXCL13
  - proteasome inhibition



SLE Clinical Trials at the U of R
B cell depletion

- Targeting B cell with anti-CD20
  - Initial studies
  - Rituximab in general lupus (Genentech; phase II/III): completed
  - Rituximab in proliferative lupus nephritis (LN) (Genentech; phase II/III): completed
  - Ocrelizumab in LN (Roche; phase III): terminated
- Anti-CD22:
  - Phase IIb trial reported superior response rates compared to placebo at week 12 in recent press release

Rituximab

Rituximab, a B-lymphocyte–depleting therapy, appears to be effective in SLE and is being investigated as a treatment for SLE and lupus nephritis. Several small case series of rituximab have shown benefit in SLE and lupus nephritis.

More recently, however, a randomized, double-blind, phase II/III trial of rituximab in moderately-to-severely active SLE failed to show differences compared to placebo, although a beneficial effect of rituximab was noted in the African American and Hispanic subgroups.

Merrill JT, Neuwelt CM, Wallace DJ, et al.. *Arthritis Rheum*. Jan 2010;62(1):222-33.

Other anti-CD20 monoclonal antibodies

Other anti-CD20 monoclonal antibodies such as ocrelizumab (humanized) and ofatumumab (human)

Other approaches to B cell modulation

- Anti-CD22
- EMBLEM Phase II study
- In patients with moderate to severe SLE, epratuzumab provided statistically significant improvements in disease activity
- In the second half of 2010, UCB will initiate two Phase III studies of epratuzumab for the treatment of patients with moderate to severe lupus.

Belimumab

Belimumab (Benlysta) is an anti–B-lymphocyte stimulator [BLyS] monoclonal antibody).

It has been found to have beneficial effects on clinical and laboratory parameters in patients with active SLE.

In addition, the number of B cells and serum IgM were reduced over time.

Belimumab was approved by the US Food and Drug Administration (FDA) for use in patients with active SLE who are autoantibody-positive and are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives, and NSAIDs.

Atacicept

Atacicept is a TACI-Ig fusion protein that inhibits BLyS and a proliferation-inducing ligand [APRIL]).

In early phase studies, atacicept was demonstrated to have biologic effects in patients with SLE, resulting in a dose-dependent reduction in B cells and immunoglobulin levels.

Abetimus

Abetimus is a B-lymphocyte tolerogen that was found to be ineffective in preventing flares of lupus nephritis in a large controlled trial, although it did reduce levels of anti-DNA antibodies.

Furie R. Abetimus sodium (riquent) for the prevention of nephritic flares in patients with systemic lupus erythematosus. *Rheum Dis Clin North Am*. Feb 2006;32(1):149-56, x.

TLR antagonists

- TLRs are key receptors of the innate immune system that can induce strong inflammatory responses- important in production of IFN
- Small molecules inhibitors of Toll-like Receptors (TLRs) 7, 8, and/or 9 are under development
- Study of DV1179, a bifunctional inhibitor of TLR7 and TLR9, starting in SLE (we will be a site)

SLE Clinical Trials at the U of R: Costimulatory blockade

- Targeting costimulation
  - CD28
    - Abatacept plus standard of care (Bristol-Myers-Squibb; phase II/III): recently completed
  - ICOSL
    - AMG557 (Amgen; phase I, now phase II)

Anticytokine therapies

Various anticytokine therapies have been proposed, including monoclonal antibodies directed against interferon-α, interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α), among others

Tumor Necrosis Factor Inhibitors

In humans, serum TNF levels are raised in SLE patients and beneficial effects of TNF inhibition have been shown in small studies.

However, long-term treatment was associated with high rates of serious adverse events.

Two large randomized trials were designed to evaluate the efficacy and safety of TNF inhibitors (infliximab, etanercept) in SLE, but both were terminated prematurely.

At the same time, TNF inhibitor use in rheumatoid arthritis can lead to formation of auto-antibodies in one-third to half of the treated patients, as well as rare cases of SLE.

Recently, a few cases of severe SLE were reported after use of TNF inhibitors for treatment of inflammatory arthritidies.In view of these findings, it is unlikely that TNF inhibition will be used routinely in SLE treatment. It has been suggested that ANA should be monitored in rheumatoid arthritis patients treated with TNF inhibitors.

Interleukin-6 Receptor Inhibitor

A phase 1 dose finding study[64] evaluated the use of a monoclonal antibody against the IL-6 receptor, tocilizumab in SLE. Sixteen patients with moderately active disease (SELENA-SLEDAI score between 3 and 10 or active glomerulonephritis) received tocilizumab in one of three doses (2, 4, and 8 mg/kg), twice weekly for 12 weeks. Tocilizumab led to reduction in inflammatory markers and auto-antibody levels. Disease activity decreased significantly (SELENA-SLEDAI from 9.5 at baseline to 5.5 at 20 weeks). Almost all patients developed dose-related neutropenia and high rates of infections were recorded.

These preliminary data are insufficient to consider the use of tocilizumab in SLE until further studies are completed

B-cell targets

Anti-CD20 antibody Rituximab	Effective in treating refractory SLE Improvements in disease activity No benefit in proliferative lupus nephritis
Ocrelizumab	No benefit in lupus nephritis
Anti-CD22 antibody Epratuzumab	Improvement in BILAG scores Reduction in corticosteroid doses with a good safety profile
B lymphocyte tolerogens Abetimus	No long-term benefit in patients with lupus nephritis
BLyS blockers Belimumab	Reduction in activity and new flares

T-cell target and costimulatory blockers

Abatacept	Improvements in non-life-threatening SLE manifestations
Efalizumab	Reduction in cutaneous SLE manifestations
Sirolimus	Safe and effective for refractory SLE

Cytokine inhibition

Anti-TNF-α Infliximab	Long-term efficacy for lupus nephritis
Anti-IFN-α/-γ Sifalimumab Rontalizumab	 No results released No results released
Anti-IL-1 Anakinra	Improvements in SLE arthritis
Anti-IL-6 Tocilizumab	Improvements in clinical and serologic responses
Anti-IL-10 B-N10[a]	Improvements in disease activity

IV IG

Iv Ig has been used in lupus induced thrombocytopenia with dramatic response

the beneficial effect is limited & its role in LN is still unclear

HDIC

High dose immunoablative chemotherapy 200mg/kg CY for 4 days followed by monthly pulse CY is found to be superior to standard method with autologous stem cell transplantation

Abou-Khamis et al Arth.Rheum, 2007

Plasmapharesis

Most impressive results are shown in active disease with minimal scaring

Its role is limited to cases resistant to steroid and immunosuppressives

Impact of pregnancy on Systemic Lupus activity.

The majority of lupus activity in pregnancy is not sever in most studies

skin, Joint and Constitutional symptoms are most commonly reported.

(Carmona 1999)

Renal worsens

Cutaneous and arthritis improves

Risk factors for increased lupus activity:

- Active lupus within 6 months before conception
- Multiple flares in the years before conception
- Discontinuation of Hydroxychloroquine

LUPUS NEPHRITIS:

Lupus nephritis appears to be more active during pregnancy. The activity is mainly mild and reversible.

However, about **12%** of patient will have irreversible progression of their renal disease. *(Petri 1994)*

The serum creatinine level normally decreases secondary to the increased glomeular filtration in healthy pregnant women.

Creatinine level that remains stable throughout pregnancy and does not decrease could be a sign of renal insufficiency.

Management of SLE Flares during Pregnancy

- Prednisone
- IV Methylprednisolone Pulse Therapy
- NSAIDs (during first trimester)
- Hydroxychloroquine (Plaquenil)

Parke, A. *J Rheumatol.* 1988;15:607-10.

Levy, RA. *Lupus.* 2001;10:401-4.

- Azathioprine (Imuran)

Ramsey-Goldman et al. *J Rheumatol.* 1993;20:1152-7.

- Cyclosporine

Hussein MM et al. *Clin Nephrol.* 1993;40:160-3.

- NO Mycophenolate Mofetil

Le Ray C, et al. *Obstet Gynecol.* 2004;103(5 Pt 2):1091-4.

* Level of Evidence: 2b

Take Home Messages

- Treatment in the future may be driven by the patient's genetic makeup: personalized medicine
- The pathogenesis of SLE is complex with dysregulation of multiple arms of the immune system
- Despite improvement in mortality, new treatments are needed given resistant disease and the side effects of current immunosuppressives
- A number of biologic molecules critical to the lupus disease process are emerging as logical targets for treatment
- Information about disease pathogenesis is leading to targeted biologic therapies

THNK YOU

Methods of monitoring in lupus nephritis

Urinalysis and microscopy: dipstick, urine cytology (sediment)

- Renal function: serum creatinine, eGFR, isotopic GFR
- Proteinuria: spot urine protein-creatinine ratio, 24-h urine protein
- Autoimmune serology: anti-dsDNA antibodies, anti-C1q antibodies, C3, C4
- Repeat renal biopsy: Histological class, AI, CI, changes of APSN
- Novel urine markers: MCP-1, TWEAK, lipocalin-2, proteomics, urine C3d

SLE Clinical Trials: Summary

- Anti-B cell
  - Rituximab studies completed
  - Ocrelizumab in nephritis on hold (Roche; phase III)
  -
- Anti-B cell growth factors
  - Belimumab in non-renal lupus (studies completed)
  - Atacicept in non-renal lupus (Serono; phase II)
- Anti-interferon α
  - Anti-interferon α (Genentech; phase II completed)
- Anti-costimulation
  - Anti-ICOSL (Amgen; completed)

www.clinicaltrials.gov

Cellular Mediated Immunity

- Via T-Cells
- ***$CD8^+$ T-Cell***
  - Stimulated ➔ Direct Killing
- ***$CD4^+$ T-Cell***
  - Th1 ➔ Stimulated ➔ Macrophage Activation
  - Th2 ➔ Stimulated ➔ B-Cell Activation